REMARKS/ARGUMENTS

The office action dated July 31, 2008 has been carefully considered. It is believed that the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Restriction/Election

As stated in our previous response, we disagree with the Examiner that claims 6 and 15 should be withdrawn as they do not relate to a non-elected invention, but rather a non-elected species. Since the election of a species does not restrict the scope of the claim, claims 6 and 15 should be retained. Similarly, the Markush group species listed in claims 12, 13 and 20 should also be retained.

35 USC §103

The Examiner has objected to claims 1-5, 7-14 and 16-20 under 35 USC §103(a) as obvious over the combined teachings from Zankel et al. (US 20050026823 A1) in view of WikiPedia (Wikimedia Foundation, Inc., see Sandhoff disease, http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008) and Jefferies et al. (U.S. Patent No. 5,981,194) and further in view of Neuwelt (U.S. Patent No. 4,866,042) and LeBowitz (USPGPB 2003/0072761 A1). We respectfully disagree with the Examiner for the reasons that follow.

The current application has an international filing date of January 10, 2003, and claims priority from a US provisional application filed on January 11, 2002. The Examiner cites Zankel et al. as the primary reference for obviousness. Zankel et al. has a filing date of June 20, 2003, which is after the filing date of the present application. Further, a request for a corrected filing receipt was filed in regard to the Zankel et al. application on October 18, 2004, requesting that the domestic priority data as claimed by the Applicant be deleted. In view of the foregoing, the earliest claim date of Zankel et al. is

after the filing date of the present application and is thus not citable under 35 USC 103(a).

Applicant respectfully submits that in the absence of this primary reference, the other references do not render the present application obvious. The previous obviousness rejection based on the combination of the remaining references, WikiPedia, Jefferies et al., Neuwelt (U.S. Patent No. 4,866,042) and LeBowitz (USPGPB 2003/0072761 A1), was indicated as withdrawn by the Examiner in paragraph 5 of the present office action. However, for the sake of completeness, Applicant repeats the comments presented in the previous response:

The cited references together fail to suggest delivering p97-conjugates to a lysosome in a cell. The cited art evidence no motivation to have combined the teachings in question in order to arrive at the claimed invention. Further, no combination of cited references could have provided a reasonable (i.e., a principled) expectation that such combination would result in claimed invention.

Neuwelt is concerned with methods to deliver "genetic material" across the blood brain barrier by chemically altering the blood brain barrier to permit passage of the material. Neuwelt's method is non-specific and allows all components that are normally excluded from the brain by the blood brain barrier to enter. While Neuwelt does disclose using its non-specific method to treat lysosomal storage diseases of the brain, nowhere does Neuwelt disclose or even remotely suggest a method involving coupling the therapeutic agent of interest to p97. Further, Neuwelt provides no teaching or suggestion that p97 could deliver therapeutics directly into a lysosome in a cell. Neuwelt is not concerned with delivery to lysosomes.

The deficiencies in Neuwelt are not remedied by Jefferies et al. Jefferies et al. teaches that p97 can be used to transport therapeutics across the blood brain barrier. Jefferies discloses that such therapeutic agents could be used to treat neurodegenerative diseases or tumors of the brain. Jefferies et al. does not disclose or suggest that p97

could deliver therapeutic agents into a lysosome in a cell. With respect, the Examiner is incorrect in stating that "Jefferies et al. also teach compositions comprising p97 and delivering it to the subject in need thereof to treat a lysosomal storage disease, i.e. Alzheimer's (Column 101, Line 25 to Column 102, Line 2). **Alzheimer's disease is not a lysosomal storage disease.** Further, the reference provided in Jefferies, column 101/102, is directed at claim 6 of the issued patent which relates to a method of diagnosing or monitoring Alzheimer's disease by detecting p97 in a sample from subject.

Based on the combined teachings of Neuwelt and Jefferies et al., one of skill in the art would **not** have a reasonable expectation that p97 could be used to target therapeutic agents to a lysosome. The ability of p97 to transport agents across the blood brain barrier is by transcytosis, wherein the agent is transported across the endothelial cells that form a barrier to a brain. Based on that mechanism of action, one could not predict whether or not p97 could also deliver agents into the lysosomes. In fact, p97 is closely related to transferrin although transferrin transports into the endosomes rather than lysosomes. Further, as the Examiner has not provided a reasonable basis by which the combination of references render the claims obvious, the objection should be removed.

The Examiner also cites LeBowitz and WikiPedia in support of the objection. However, both of these references are specific references on Sandhoff disease which merely teach that Sandhoff disease is the result of the absence or defect in the presence of β-hexosaminidase. Applicant does not dispute that the deficiency in Sandhoff disease was known in the art and that it would be desirable to provide β-hexosaminidase to a person with Sandhoff disease. However, these references failed to provide any suggestion or motivation to couple the therapeutic enzyme to p97 in order to facilitate transport into the lysosomes. In fact the major issue in treating this disease is that enzymes are not targeted for delivery to the brain for overcoming the neurological effects of the disease. Therefore it is not obvious that p97 can transport enzymes

across the blood brain barrier **and** deliver the enzymes to the lysosomes of the affected neurons therein.

In view of the foregoing, we respectfully request that the objection to the claims under 35 USC §103 be withdrawn.

The Commissioner is hereby authorized to charge any fee (including any claim fee) which may be required to our Deposit Account No. 02-2095.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact the undersigned by telephone at (416) 957-1682 at her convenience.

Respectfully submitted,

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